REMARKS

This Response is being filed in connection with the Notice of Non-Compliant Amendment mailed May 14, 2010. In that Notice, it was noted that the amended paragraphs do not include markings. The Applicant submits this Response with a five-month extension of time to supply the correctly marked paragraphs.

* * *

Upon entry of the present amendment, claims 1, 3 to 5, 9, 10, 23 26 and 27 are pending. Claim 23 has been withdrawn from consideration. Claim 6 has been cancelled herein without prejudice. Applicants maintain the right to file the cancelled claim(s) in any related application claiming the benefit of priority of the subject application. Accordingly, claims 1, 3 to 5, 9, 10, 26 and 27 are under consideration. Applicants respectfully request examination and an action on the merits.

Regarding the Claim Amendments

The amendments to the claims are supported throughout the specification. In particular, support for the amendments to claims 1, 3 and 4 to recite "archaeal family B DNA polymerase" or "family B" can be found, for example: at page 3, lines 3 and 4; page 13, lines 1 and 2; page 17, lines 2 and 3, Example 1; and, in Figure 1 of the specification as filed. Support for the amendment to claims 1, 4, 9 and 10 to recite "V93 substitution" or "substitution" can be found, for example: at page 5 lines 12, 18 to 20; at page 8, lines 5 and 8; at page 11, line 1; at page 15, lines 10 and 19 (Figure 4 description), at page 16, line 13, (Figure 5 description); at page 21, lines 4, 14 to 15 and page 22, lines 10 to 12 (Example 2); at page 23, line 13 (Table 1); at page 24, lines 13 to 16; at page 25, lines 13 to 14; and, in claim 6 as originally filed.. Support for amendments to claims 4 and 5 to recite "highly conserved region of the uracil-binding pocket" and "Region B" respectively can be found, for example: at page 4, lines 21 to 28and, page 5, lines 7 to 8. Subject matter from dependent claim 6 has been incorporated into claim 1and claim 6 has been cancelled. As the amendments to the claims are supported by the specification, no new matter has been added and entry thereof is respectfully requested.

Regarding the Information Disclosure Statement (IDS)

Applicants acknowledge the Examiner's comments regarding the Information Disclosure Statement and note that certain references cited in the specification were not previously submitted in an IDS. To that end, submitted herewith is an IDS with copies of publications cited in the specification and listed in the attached PTO-1449 Form. Applicants respectfully request consideration of the accompanying publications and return of an initialed copy of the PTO-1449 by the Examiner to the undersigned indicating that the publications have been considered.

Regarding the Amendments to the Specification

The Specification has been amended to correct informalities. Specifically, sequence identification numbers (SEQ ID NOs) for amino acid sequences shown in Figure 1 and Figure 2 as they correspond to the amino acid sequences set forth in the Sequence Listing have been added to the first paragraph on page 13 and the paragraph bridging pages 13 and14, namely paragraphs describing Figure 1 and Figure 2 respectively. Embedded hyperlinks have also been removed from the Figure 1 and Figure 2 paragraph descriptions on pages 13 and 14. Additionally, a journal title has been amended to correct a duplicate citation error in the paragraph on page 17. As such, no new matter has been added and entry of the amendments is respectfully requested.

Regarding the Objection to the Specification

The objection of the Specification due to an absence of sequence identifiers for specific amino acid sequences disclosed therein, namely the amino acid sequences shown in Figure 1 and Figure 2, is respectfully traversed. Figure descriptions, in the Specification, for both Figure 1 and Figure 2 have been amended to provide SEQ ID NOs for the corresponding amino acid sequences shown in Figure 1 and Figure 2, as set forth in the Sequence Listing. As such, the objection is moot.

REJECTIONS UNDER 35 U.S.C. §112, FIRST PARAGRAPH

Written Description

The rejection of claims 1, 3 to 5, 9, 10, 26 ad 27 under U.S.C. §112, first paragraph as allegedly lacking an adequate written description is respectfully traversed. The grounds for rejection are set forth in the Office Action, pages 3-5.

The claims prior to and following entry of the amendments are adequately described under 35 U.S.C. §112, first paragraph. Nevertheless, solely in order to further prosecution of the application and without acquiescing to the propriety of the rejection, the claims have been amended as set forth above. The rejection will therefore be addressed as if applied to the amended claims.

Firstly, Applicants note that the written description requirement under 35 U.S.C. §112, first paragraph is "to clearly convey the information that an applicant has invented the subject matter which is claimed." *In re Barker*, F.2d 588, 592 (CCPA 1977). A proper analysis for written description under 35 U.S.C. §112, first paragraph is whether one skilled in the art can reasonably conclude that the inventor had possession of the claimed invention. See, e.g., *Vas-Cath, Inc. v. Mahurkar*, 935 F.2d 1555, 1563 (Fed. Cir. 1991); see, also, *Ralston Purina Co. v. Far-Mar-Co, Inc.*, 772 F.2d 1570, 1575 (Fed. Cir. 1985). Possession is assessed from the viewpoint of one of ordinary skill in the art: "Satisfaction of this requirement is measured by the understanding of the ordinarily skilled artisan." *Lockwood v. Am. Airlines, Inc.*, 107 F.3d 1565, 1572 (Fed. Cir. 1997). The description needed to satisfy the requirements of 35 U.S.C. §112 "varies with the nature and scope of the invention at issue, and with the scientific and technologic knowledge already in existence.....Since the law is applied to each invention in view of the state of the relevant knowledge, its application will vary with differences in the state of the knowledge in the field and differences in the predictability of the science....the law must take cognizance of the scientific facts." *Capon v. Eshhar*, 418 F.3d , 1349, 1357 (Fed. Cir. 2005). Thus, an adequate written description is a factual inquiry measured by one of ordinary skill in the art, that varies with the nature and scope of the invention, taking into consideration the scientific and technologic knowledge in existence in the relevant field.

Furthermore, to satisfy the written description requirement, "Applicants are not required to disclose every species encompassed by their claims, even in an unpredictable art." *In re Angstadt*, 537 F.2d 498, 502-503 (CCPA 1976), *Utter v. Hiraga*, 845 F.2d 993, 998-99 (Fed. Cir.

1988). Again, to satisfy the written description requirement, an applicant "must also convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention." *Vas-Cath, Inc. v. Mahurkar*, 935 F.2d 1555, 1563-64 (Fed. Cir. 1991). Possession may be shown by "any description of sufficient, relevant, identifying characteristics so long as a person skilled in the art would recognize that the inventor had possession of the claimed invention." *Purdue Pharma L.P. v. Faulding Inc.*, 230 F.3d 1320, 1323 (Fed. Cir. 2000). The applicant, however, "does not have to describe exactly the subject matter claimed." *In re Gosteli*, 872 F.2d 1008, 1012 (Fed. Cir. 1989)

Moreover, a description of a genus may be achieved by a representative number of species falling within the scope of the genus **or** of a recitation of structural features common to the members of the genus, which constitute a substantial portion of the genus. *Reagents of the Univ. Calif. v. Eli Lilly* 119 F.3d 1559, 1568 (Fed. Cir. 1997), Emphasis added. For biological molecules, identifying characteristics can include, *inter alia*, sequence, structure and length. Although courts have not specified a minimum number of species constituting a representative number, or structural features common to the genus, an adequate written description does not require the disclosure of every species encompassed by the claims, even in an unpredictable art. *In re Angstadt*, 537 F.2d 498, 502-503 (CCPA 1976), Emphasis added. In *Lilly*, the court reiterated that "every species in a genus need not be described in order that a genus meet the written description requirement." *Id.* (*citing Utter v. Hiraga*, 845 F.2d 993, 998-99 (Fed. Cir. 1988)). Thus, a description of every variant arcahaeal family B DNA polymerase or every modified residue of the variant arcahaeal family B DNA polymerase is clearly not required in order to satisfy the written description requirement of 35 U.S.C. §112, first paragraph.

Here, in view of the guidance in the specification and knowledge in the art at the time of the invention, numerous structural features of variant archaeal family B DNA polymerases would be known to the skilled artisan. Thus, the skilled artisan would be apprised of sufficient relevant identifying characteristics of a variant archaeal family B DNA polymerase genus. In addition, the skilled artisan would know of numerous variant archaeal family B DNA polymerases having reduced affinity for uracil and, therefore, a representative number of variant archaeal family B DNA polymerases having reduced affinity for uracil than the wild-type

polymerase.

Secondly, concerning the allegations set forth in the Office Action which states, "Thus the claimed variant archaeal DNA polymerase lacks sufficient structure to adequately describe the [sic] those variant archaeal polymerases encompassed by the claims. The Specification, however, only provides a single representative species of variant archaeal DNA polymerase....There is no disclosure of any particular structure to function activity in the single disclosed species. The specification also fails to describe additional representative species of these variant polymerases by any identifying structural characteristics or properties other than the activities recited in claims 1, for which no predictability of structure is apparent" (second paragraph, Office Action, page 4) Applicants respectfully disagree for at least the following reasons set forth in the paragraphs below.

The Specification in several instances provides representative variant family B archaeal DNA polymerases, including references to their structure, their specific activity and ability to bind uracil. At first issue, the Specification, at page 3. line 3 and in Figure 1, provides several wild type archaeal DNA polymerases which can be modified to produce the variant archaeal DNA polymerases, "The variant DNA polymerase may be a modification of an arcahaeal family B DNA polymerase. For instance the variant may be derived from any one of the fourteen archaeal family B DNA polymerase shown in Figure1." Further, the Specification provides amino acid sequences of the fourteen archaeal family B DNA polymerases (Figure 1) and sequence alignment data –determined in Example 2– for the polymerases. In particular the sequence alignment data show the N-terminal domains of several archaeal family B DNA polymerases (please see page13, line 1 to 16; page 20, lines 19 to 24; Example 1, and Figure 1), as they correspond to residues of 1-130 of pyrococcus furiosus polymerase, namely portions of the archaeal family B DNA polymerase sequences characterized as having highly conserved residues in two regions: Region A and Region B of the uracil pocket. In this regard, the Specification further describes the structure of the uracil pocket characterized by the conserved residues within Region A and Region B that can be modified to produce the claimed variants:

"The inventors have found (see Example 1) that a uracil-binding pocket of the wild type

polymerase forms part of the ssDNA template binding cleft of the polymerase (the so call cleft T). Furthermore the uracil-binding pocket comprises amino acids from two conserved regions of the polymerases: Region A and Region B separated by an unconserved region. In the archaeal polymerase from *Pyrococcus furiosus* (Pfu-Pol) Region A is formed by the amino acids 1-40 and Region B by amino acids 78-130. Highly conserved residues in these two regions form the highly ordered uracil-binding pocket. Other Achaea have similar regions A & B in their respective polymerases as illustrated in Figure 1. Preferably, one or more of the amino acids in Regions A and/or B are altered to form the variant archaeal DNA polymerase.

Figure 1 illustrates a sequence alignment of the N -terminal domains of various archaeal polymerases. In figure 1 amino acids designated (1) have 90% or greater identity, (2) indicates 80- 90% identity and (3) 60-80% identity. The two highly conserved regions that form the uracil binding pocket are:

Region A, amino acids 1-40 in Pfu-Pol (and corresponding regions in the other polymerases); and

Region B, amino acids 78-131 in Pfu-Pol (and corresponding regions in the other polymerases).

It is preferred that the variant is formed by alteration of one of the amino acids block shaded (1, 2 or 3) in Figure 1....(please see page 4, lines 19 to 28 and Example 1)

At second issue, the Specification identifies several specific single amino acid residues which can be altered to effect the conformation of the uracil pocket and thereby reduce its uracil-binding ability (see page 5, lines 15 to 20; page 8 lines 1 to 9). Furthermore, the Specification also identities residues that can be mutated in other species: "It will be appreciated that equivalent residues in other archaeal polymerases may be mutated (see Figure1)" and provides examples of the preferred mutants (see page 8, lines 7 to 9). At third issue, Applicants note that data for specific activity and uracil binding abilities for several variant archaeal Family B DNA polymerases is also provided in the Specification (See Table1, and Example 2).

In addition, to the guidance in the Specification (discussed above), Applicants note that knowledge of the archaeal family B DNA Polymerases as group of related DNA polymerases was well established at the time of invention. Furthermore, crystal structures of several archaeal family B DNA polymerases and protein modelling techniques for use in site directed mutagenesis experiments were also known in the art at the time of the invention . As evidence of this knowledge, exhibits A, B, C, D, and E [Hopfner et al., *PNAS* 96:3600 (1999); Zhao et al ., *Structure* 7:1189 (1999); Rodriguez, et al., *Mol. Biol.* 299:447 (2000); H. Hashimoto et al., *J. Mol. Biol.* 306: 469 (2001), Guex, N. and Peitsch, M, *Electrophoresis* 18:2714 (1997)] all of which are referenced in the specification, are hereby submitted. Exhibits A to D describe crystal structures of archaeal family B DNA polymerases, namely *Thermococcus gorgonarius* (Tgo-Pol) (Exhibit A), *Desulfurococcus* strain Tok (DTok-Pol) (Exhibit B), *Thermococcus sp.* 9°N-7 (9°N-7-Pol) (Exhibit C) and *Pyrococcus kodakaraensis* KOD1 (KOD1-Pol) (Exhibit D). Exhibit E describes protein modeling techniques used to assist in the design of mutagenesis studies. Thus, in view of the guidance in the specification and knowledge in the art, one skilled in the art would know of structural features shared among the archaeal family B DNA polymerases, as well as specific amino acid residues of the uracil-binding pocket in the wild-type polymerases which could be modified to produce a variant archaeal family B DNA polymerase having a V93 substitution of a wild-type archaeal family B DNA polymerase amino acid sequence, the substitution being in the amino-terminal amino acids that comprise a uracil-binding pocket in the wild-type polymerase whereby the variant polymerase has reduced affinity for uracil than the wild-type polymerase.

In sum, in view of the guidance in the specification and the high level of knowledge and skill in the art at the time of the invention, the skilled artisan could readily produce the claimed variant archaeal family B DNA polymerases and kits. Consequently, claims 1, 3 to 5, 9, 10, 26 ad 27 are adequately enabled under 35 U.S.C. §112, first paragraph, and the rejection must be withdrawn.

Enablement

The rejection of claims 1, 3 to 5, 9, 10, 26 ad 27 under U.S.C. §112, first paragraph as allegedly lacking enablement is respectfully traversed. The grounds for rejection are set forth in

the Office Action, pages 5 to 8.

The claims prior to and following entry of the amendments are enabled under 35 U.S.C. §112, first paragraph. Nevertheless, solely in order to further prosecution of the application and without acquiescing to the propriety of the rejection, the claims have been amended as set forth above. The rejection will therefore be addressed as if applied to the amended claims.

The claims as amended are directed toward variant archaeal family B DNA polymerases having a V93 substitution of a wild-type archaeal family B DNA polymerase amino acid sequence, whereby the variant polymerase has reduced affinity for uracil than the wild-type polymerase. In view of the guidance in the specification and knowledge in the art at the time of the invention, the claimed variant archaeal family B DNA polymerases having the requisite reduced affinity for uracil could be produced and identified using routine methods disclosed in the specification, or known in the art at the time of the invention without undue experimentation.

In view of the foregoing, the claims 1, 3 to 5, 9, 10, 26 ad 27 are adequately enabled. Accordingly, Applicants respectfully request withdrawal of the enablement rejection under 35 U.S.C §112, first paragraph.

CONCLUSION

In summary, for the reasons set forth herein, Applicants maintain that the claims clearly and patentably define the invention, respectfully request that the Examiner reconsider the various grounds set forth in the Office Action, and respectfully request the allowance of the claims which are now pending.

If the Examiner would like to discuss any of the issues raised in the Office Action, Applicant's representative can be reached at (213) 488-7100.

Please charge any fees associated with the submission of this paper to Deposit Account Number 033975. The Commissioner for Patents is also authorized to credit any over payments to the above-referenced Deposit Account.

Respectfully Submitted,

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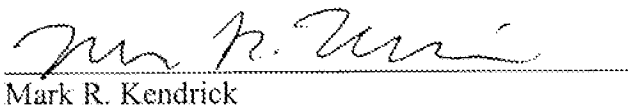

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